AstraZeneca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **ROBERTS ET AL.**	Filed: **November 17, 2003**
Application No: **10/714,447**	Attorney Docket No.: **A1479-3P US**
Art Unit: **1624**	Examiner: **Emily Bernhardt**
Title: **Novel Compounds with Analgesic Effects**	

MAIL STOP **APPEAL BRIEF-PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF PURSUANT TO 37 CFR 41.37

(1) REAL PARTY IN INTEREST

The real party in interest in this appeal is AstraZeneca Canada Inc. having a principal place of business at 1004 Middlegate road, Mississauga, Ontario L4Y 1M4, Canada. AstraZeneca Canada Inc. is the assignee and owner of the entire interest in the above identified application by virtue of a series of assignments recorded in the United States Patent and Trademark Office on 1) April 24, 1997 at Reel/Frame 9531/0722, 2) September 24, 1998 at Reel/Frame 9232/0471, and 3) October 12, 2000 at Reel/Frame 011217/0591.

(2) RELATED APPEALS AND INTERFERENCES

The undersigned knows of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) STATUS OF THE CLAIMS

Claim 19 stands rejected and is the subject of this appeal.

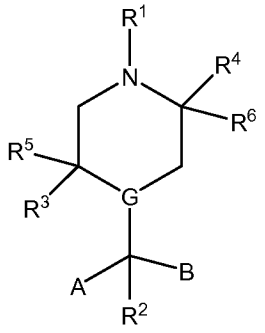
Claims 1-18 have been canceled.

(4) STATUS OF AMENDMENTS FILED SUBSEQUENT TO THE FINAL REJECTION

There have been no amendments filed subsequent to the Final rejection mailed February 16, 2006.

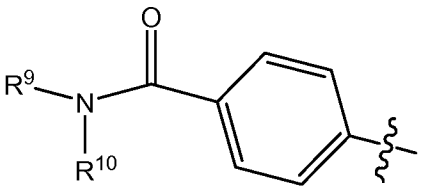
(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter that forms the basis of this appeal is directed to piperazinyl compounds useful for binding to delta opioid receptors and treating pain represented by formula (I):



wherein G is a nitrogen atom;

A is:



wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH_3, CF_3 and halogen;

R^1 is selected from the group consisting of: H; a branched or straight C_1–C_6 alkyl; –$CO(C_1$–C_6 alkyl); and (C_1–C_6 alkyl)-B' wherein B' is a C_6, C_9 or C_{10} aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C_6, C_9 or C_{10} aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH_3 or halogen;

R^2 is selected from the group consisting of H and CH_3;

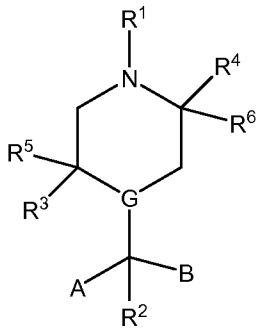
R^9, and R^{10}, are selected from the group consisting of H, a branched or straight C_1–C_6 alkyl and a C_2–C_6 alkenyl;

B is an C_6, C_9 or C_{10} aromatic; or a C_6, C_9 or C_{10} hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$ and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are selected from: H; a branched or straight C_1–C_6 alkyl; or –CO(C_1–C_6 alkyl); and

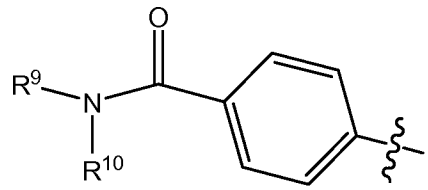
R^3, R^4, R^5, and R^6 are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof.



Formula (I) is described, for example, at page 3, lines 1-5.

G is N (nitrogen) is described, for example, at page 9, line 5 and Examples 1-48 and 50-56.



A is is described, for example, at page 6, lines 8-24; page 9, lines 6-10; and Examples 21-39, 42, and 49-51.

The R^1 that is selected from the group consisting of H; a branched or straight C_1–C_6 alkyl; –CO(C_1–C_6 alkyl); and (C_1–C_6 alkyl)-B' is described, for example, at page 4, lines 13-20; page 7, lines 1-4; page 9, line 18; and Examples 1, 4, 7, 12, 13, 18, 21, 23, 25, 27-31, 34, 35, 37, 38, 40, 42, 43, 45-50, and 51-56.

The B' that is a C_6, C_9 or C_{10} aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C_6, C_9 or C_{10} aryl and the 5 or 6-membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH_3 or halogen is described, for example, at page 4, line 14 and page 5, lines 5-10; page 7, lines 2 and 11-20; and Examples 52-56.

The R^2 that is selected from the group consisting of H and CH_3 is described, for example, at page 4, line 24; page 7, line 6; page 9, line 20; and Examples 1-56.

The R^9 and R^{10} that are selected from the group consisting of H, a branched or straight C_1–C_6 alkyl and a C_2–C_6 alkenyl are described, for example, at page 5, line 1

and page 4, lines 13-20; page 7, lines 1-4 and 8-9; page 9, line 16; and Examples 21-39, 42, and 49-51.

The B that is a C_6, C_9 or C_{10} aromatic; or a C_6, C_9 or C_{10} hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$ and $(CH_2)_pSO_2NR^7R^8$ is described, for example, at page 5, lines 5-10; page 7, lines 11-20; page 10, lines 1-10; and Examples 1-56.

The p that is 0, 1, or 2 is described, for example, at page 5, line 12; page 10, line 19; and Examples 1-56.

The R^7 and R^8 that are selected from: H; a branched or straight C_1–C_6 alkyl; or –$CO(C_1$–C_6 alkyl) are described, for example, at page 4, lines 13-22; page 7, lines 1-4; page 10, line 12 and page 9, line 18; and Examples 1-20, 31-34, 38-41, and 50-51.

The R^3, R^4, R^5, and R^6 that are each H are described, for example, at 21-30, 35-36, and 42-56.

The pharmaceutically acceptable salts of Formula (I) are described, for example, at page 6, lines 1-2 and page 85, lines 13-24.

The hydrates of Formula (I) are described, for example, at page 6, lines 1-2.

The isoforms of Formula (I) are described, for example, at page 6, lines 1-2 and page 11, lines 16-17.

The isomers, other than positional isomers, of Formula (I) are described, for example, at page 6, lines 1-2 and page 11, lines 12-14.

(6) GROUNDS OF REJECTION PRESENTED FOR REVIEW

a. 35 U.S.C. § 103(a)

Claim 19 stands rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Calderon et al. and Bilsky et al. references in view of Chang et al. (PCT Publication WO93/15062 or U.S. Pat. No. 5,658,908, applied as of its § 102(e) date).

b. Obviousness-Type Double Patenting Rejection

Claim 19 stands rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. patent No. 6,696,447.

(7) ARGUMENTS

I. The Examiner has failed to establish a prima facie case of obviousness because there is no motivation or suggestion to modify and/or combine the reference's on which the Examiner relies.

The full citations for the Calderon et al. and Bilsky et al. references are set forth in Appendix D submitted herewith. The Calderon et al. and Bilsky et al. references were cited as C1, C2, C4, and C5 in the Information Disclosure Statement submitted by Applicants on November 17, 2003.

In the March 22, 2005 final office action, the Examiner asserted on page 2 that the presently claimed compounds of formula (I) are obvious variants over Calderon et al. and Bilsky et al. in view of Chang et al. because Chang et al. supposedly teaches that the hydrogen and methyl on the piperazine ring carbons of Chang et al. are interchangeable in similar compounds having the same use as described in Chang et al. The Examiner supported this notion of interchangeability by pointing to disclosures in Chang et al. that allegedly indicate R3-R5 can be either hydrogen or methyl; R6 can be hydrogen, alkyl, cycloalkyl, or arylalkyl; and that the "instant compounds are within the preferred embodiments taught in col. 6." See, Final Office Action dated March 22, 2005, at pages 2-3. The Examiner concluded that the interchangeability allegedly taught by Chang et al. was akin to an "equivalency teaching" and therefore "it would have been obvious to one skilled in the art at the time the instant invention was made to replace the aforementioned groups in …[Bilsky et al. and Calderon et al.] with those present herein at instant R1 and R3-R6 and in so doing obtain additional compounds for treating pain …." See, Final Office Action dated March 22, 2005, at page 3.

The Calderon et al. and Bilsky et al. references only disclose compounds having dimethyl groups substituted on the carbons of the central piperazine ring. In fact, under the heading "Chemistry" at page 696 in the Calderon et al. reference identified as C5 in Applicants' IDS, Calderon et al. expressly emphasizes the importance of using a dimethyl substituted intermediate, which is chiral due to the dimethyl substitution, to synthesize the dimethyl substituted final product. But for the dimethyl group on the piperazine ring, the intermediate used by Calderon et al. would have been achiral and the resulting products would not have been readily separable and optically pure.

In contrast, Claim 19 of Applicants' claimed invention is directed to compounds containing an unsubstituted central piperazine ring, wherein Claim 19 defines the R^3, R^4, R^5,

and R^6 substituent groups of formula (I) so as to limit such groups to hydrogen. The Examiner acknowledges this difference on page 2 of the Final Office Action, but proposes that Calderon et al. and Bilsky et al. be combined with Chang et al. to eliminate the dimethyl substituents on the central piperazine of the Bilsky et al. and Calderon et al. references.

Applicants, however, respectfully disagree with the Examiner's proposition because Chang et al. does not teach that hydrogen and methyl behave equivalently and are therefore readily interchangeable. Indeed, at the time the present application was filed, a person of ordinary skill in the art upon viewing Chang et al. as a whole would not have been motivated to modify the compounds disclosed in Calderon et al. and/or Bilsky et al. so as to arrive at the presently claimed compounds. In fact, it would have been reasonable for a person of ordinary skill in the art when viewing Calderon et al.'s and Bilsky et al.'s dimethylated piperazinyl compounds in light of Chang et al.'s own preference for methylated piperazinyl compounds to have understood Chang et al.'s express statements to mean that methyl and hydrogen did not behave equivalently and—contrary to the Examiner's position—were not interchangeable. Chang et al. stated during prosecution of U.S. Pat. No. 5,658,908 (hereinafter "the '908 patent") that methyl and hydrogen did not behave equivalently and Bilsky et al.'s and Calderon et al.'s preference for dimethylated piperazinyl compounds seemingly validated Chang et al.'s nonequivalency statement. As a result, in contrast to the Examiner's assertions, the person of ordinary skill in the art upon viewing Chang et al. as a whole would have been motivated to retain the methyl groups on the piperazinyl of the Bilsky et al and/or Calderon et al. compounds.

As the Federal Circuit explained in the recently decided Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd. case, a prima facie case of obviousness regarding a structurally similar claimed and prior art compound is only made out when the prior art gives reason or motivation to make the claimed compound. No. 06-1329, 2007 U.S. App. LEXIS 15349, at *11, 83 U.S.P.Q.2D 1169, 1174 (Fed. Cir. June 28, 2007). The court further explained that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." Id. at *11, 83 U.S.P.Q.2D at 1174. The court noted that a prima facie case of obviousness can be based on structural similarity where the structural relationship may provide the requisite motivation or suggestion to modify the known compound to arrive at the claimed compound. Id. at *11-12, 83 U.S.P.Q.2D at 1174. The court noted that while a "known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds

with improved properties'", it still remained necessary "in cases involving new chemical compounds … to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound." Id. at *12, 83 U.S.P.Q.2D at 1174. The Federal Circuit went on to confirm that the test for establishing a prima facie case of obviousness of a structurally similar claimed and prior art compound as set forth hereinabove is consistent with the legal principles set forth in the recently decided Supreme Court case, KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). Id. at *12, 83 U.S.P.Q.2D at 1174.

In the case at hand, Chang et al. expressly stated during the prosecution of the '908 patent that methyl and hydrogen did not behave equivalently and therefore were not readily interchangeable. More specifically, Chang et al. stated in relevant part in reliance on a 132 declaration as follows:

> Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, *comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity*. (Emphasis added).

(See page 60 of the February 9, 1996 response attached hereto as Appendix B and made of record in Applicants' November 30, 2005 response.) As the scope and content of prior art includes the prosecution history associated with the prior art, Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd, No. 06-1329, 2007 U.S. App. LEXIS 15349, at *32-34; 83 U.S.P.Q.2D 1169, 1179 (Fed. Cir. June 28, 2007), and Chang et al.'s own words clearly indicate Chang et al. did not believe methyl and hydrogen behaved equivalently and were therefore readily interchangeable, a person of ordinary skill in the art upon viewing Chang et al. as a whole would not have been motivated to modify the compounds disclosed in Bilsky et al. and/or Calderon et al. so as to arrive at the presently claimed compounds.

This conclusion is further buttressed by Chang et al.'s repeated statements throughout the specification of the '908 patent that the preferred compounds that exhibit delta-opioid and/or mu-opioid agonist activity have methyl substituted on the piperazinyl ring at at least one of the R^3, R^4 and R^5 positions. (See, col. 5, lines 36-38; col. 6, line 20 to column 7, line 17; col. 18, line 65 to col. 19, line 54; col 19, line 66 to col. 20, line 50; col. 20, line 62 to col. 22, line 16; col.

23, lines 3-18; col. 24, line 10 to col. 25, line 8; and col. 112, lines 25-29 of the '908 patent). And yet further buttressed by the fact that the Example 1-50, 53-76, and 78-91 compounds disclosed by Chang et al. are substituted on the piperazinyl ring by 2 or more methyl groups. Specifically, Examples 1-11, 14-33, 35-38, and 40-91 contain a dimethyl substituted piperazinyl ring, while Examples 12, 13, 34, and 39 contain a trimethyl substituted piperazinyl ring. Please note, Examples 51, 52, and 77 contain piperidinyl—not piperazinyl—rings. And even yet further buttressed by the fact that the "particularly preferred compounds" identified by Chang et al. at col. 15, lines 17-22 of the '908 patent all have a dimethyl substituted piperazinyl ring.

For all of the reasons set forth hereinabove, it would have been reasonable for a person of ordinary skill in the art when viewing Calderon et al.'s and Bilsky et al.'s dimethylated piperazinyl compounds in light of Chang et al.'s own preference for methylated piperazinyl compounds to have understood Chang et al.'s express statements to mean that methyl and hydrogen did not behave equivalently and—contrary to the Examiner's position—were not interchangeable. Chang et al. stated that methyl and hydrogen did not behave equivalently and Bilsky et al.'s and Calderon et al.'s preference for dimethylated piperazinyl compounds seemingly validated Chang et al.'s nonequivalency statement. As a result, Applicants respectfully assert that Calderon et al., Bilsky et al. and Chang et al. all lacked the requisite suggestion and/or motivation to eliminate the methyl groups from the carbons of the central piperazinyl of the Calderon et al. and/or Bilsky et al. compounds so as to arrive at Applicants' claimed invention. Accordingly, claim 19 is not obvious over Bilsky et al. and Calderon et al. in view of Change et al.

In sum, a person of ordinary skill in the art upon reading Bilsky et al., Calderon et al., and/or Chang et al. as a whole would not have been motivated at the time the present application was filed to replace the methyl groups of the dimethylated compounds of Calderon et al. or Bilsky et al. with the hydrogens of Chang et al. because Chang et al.'s own words indicated methyl and hydrogen do not behave equivalently and are therefore not readily interchangeable. Accordingly, Applicants respectfully submit that the Examiner made clear errors and/or omitted one or more essential elements needed to establish a prima facie case of obviousness, and therefore respectfully request that the Examiner's rejection of claim 19 as obvious over Calderon et al. and Bilsky et al. in view of Chang et al. be reversed.

II. Terminal Disclaimer Submitted Herewith Renders Obviousness-type Double Patenting Rejection over Claims of U.S. Patent No. 6,696,447 Moot.

Applicants respectfully submit herewith in Appendix B a terminal disclaimer as to U.S. Patent No. 6,696,447. As a result, the obviousness-type double patenting rejection over the claims of the '447 patent has been rendered moot. Accordingly, Applicants respectfully request the withdrawal of this rejection.

Respectfully submitted,

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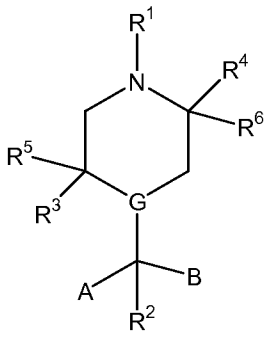
Dated: December 3, 2007
Reg. No: 51,574

APPENDIX A
COPY OF CLAIM INVOLVED IN APPEAL

Claims 1-18. (Cancelled).

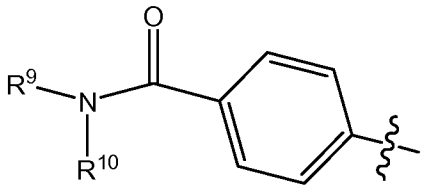
19. A compound of formula (I)



(I)

wherein G is a nitrogen atom;

A is:



wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH_3, CF_3 and halogen;

R^1 is selected from the group consisting of: H; a branched or straight C_1–C_6 alkyl; –CO(C_1–C_6 alkyl); and (C_1–C_6 alkyl)-B' wherein B' is a C_6, C_9 or C_{10} aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C_6, C_9 or C_{10} aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH_3 or halogen;

R^2 is selected from the group consisting of H and CH_3;

R^9, and R^{10}, are selected from the group consisting of H, a branched or straight C_1–C_6 alkyl and a C_2–C_6 alkenyl;

B is an C_6, C_9 or C_{10} aromatic; or a C_6, C_9 or C_{10} hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$ and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are selected from: H; a branched or straight C_1–C_6 alkyl; or –CO(C_1–C_6 alkyl);

R^3, R^4, R^5, and R^6 are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof.

APPENDIX B

EVIDENCE APPENDIX

I. Excerpt from Chang et al.'s February 9, 1996 response

Please see comments made in Chang et al.'s February 9, 1996 response attached hereto and identified with the "Appendix I" heading. The attached pages 1 and 58-63 from Chang et al.'s February 9, 1996 response and attached pages 1-5 from the 132 declaration submitted with Chang et al.'s February 9, 1996 response were made of record in Applicants' November 30, 2005 response.

II. Terminal Disclaimer—U.S. Patent No. 6,696,447

Please find attached hereto a terminal disclaimer disclaiming the terminal part of the statutory term of any patent granted on the instant application that would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior patent No. 6,696,447, except as provided in the terminal disclaimer attached hereto.

Appendix I

Patent Application
3022-107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al.

Group Art Unit: 1202

Application No. 08/284,445

Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: **"OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature

MARY B. CARUSO
Name of Person Mailing This Paper

FEBRUARY 9, 1996
Date of Mailing

EF561241830US
Express Mail Label Number

AMENDMENT RESPONDING TO AUGUST 9, 1995 OFFICE ACTION IN U.S. PATENT APPLICATION NO. 08/284,445

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the 9 August 1995 Office Action in the above-identified application, please amend the application, as follows:

In the Claims

Amend the claims as follows:

The Examiner has requested the month of publication for references BD-BH, which are as follows. BD: November, 1993; BE: October, 1993; BF: November, 1993; BG: November, 1993; BH: November, 1993.

Claims 1-8, 12-14, 38-40 and 44 were rejected in the 9 August 1995 Office Action as being drawn to improper Markush group(s) on the basis that the variables G, R^9 and R^{10} embrace more than one invention as discussed in the restriction requirement.

In the restriction requirement dated April 5, 1995, the Examiner sought to limit claim 1 to G=N and exclude R^9 and R^{10} from being C_3 and higher. Applicants respectfully disagree with this suggestion, particularly since the claims have already been examined on the merits. Furthermore, according to M.P.E.P. Section 803,

> "[i]f the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to distinct or independent inventions."

Thus, since examination on the merits has already occurred, it is clear that the Markush groups of the claims are in proper form according to the M.P.E.P.

For the foregoing reasons, the Section 112 rejections have been overcome, as described in the above discussion, and through the foregoing amendments, which serve to clarify claims 1, 5, 7, 12, 14-17, 38 and 44.

Arguments for Patentability

As discussed above, references AM, AS-AU and BD-BH do not qualify as prior art.

Claims 1, 3, 14-17 and 38-40 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 102(b) over references AW and AY. Furthermore, claims 20, 21 and 24 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 103 over references AW and AY.

AW and AY are directed to a calcium antagonist, KB-2796, which is I-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride. Related compounds A, B, C, Flunarazine and Cinnarizine are also discussed. (See the structural configurations in AW, Figure 1 and AY, Table 1.) None of the compounds discussed in AW or AY teach or suggest the compounds of the present invention.

Instead, the present invention, as claimed, is related to opioid diarylmethylpiperazines and piperidines. The claims of the present invention, as amended, are directed to diarylmethylpiperazines and piperidines having a particular type of substituent attached to at least one of the carbon atoms in the piperazine ring. For example, according to claim 1, as amended, the substituents on the piperazine are as follows:

> "R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms."

In contrast, AW and AY do not teach or suggest such compounds having a substituent attached to at least one of the carbon atoms in the piperazine ring.

132 ?.

According to the enclosed Declaration under 37 C.F.R. 1.131 by Dr. Robert McNutt, comparisons have been made between compounds that have a substituent attached to at least one of the carbon atoms in the piperazine ring and those that do not, using the assay procedures set out in Example 92 on pages 156-157 of the specification.

Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity.

The compounds tested were as follows, wherein Compounds 1-4 have no substituents on carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on carbon atoms of the piperazine ring:

Compound 1: (+)-3-(-‡-(4-Allyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 1a: (+)-3-((‡R*)-‡-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (+)-3-(‡-(4-Allyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 2a: (±)-3-((‡R*)-‡-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (±)-3-(‡-(4-Allyl-1-piperazinyl)benzyl)phenol;

Compound 3a: (±)-3-((‡R*)-‡-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (±)-3-(‡-(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (±)-3-((‡R*)-‡-((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

The compounds having methyl groups on the piperazine ring can be found in the present specification as follows. Compound 1a can be found, for example, on page 12, number 1. Compound 2a can be found, for example, on page 14, number 40. Compound 3a can be found, for example, on page 15, number 47. Compound 4a can be found, for example, on page 21, number 136.

The test results for Compounds 1-4 and Compound 1a-4a using assays described in Example 92 on pages 156-157 of the specification are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

nd = not determined

* Test results showed that Compound 2 has antagonist activity rather than agonist activity in the mouse vas deferens assay

According to Dr. McNutt's Declaration, the test results show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

Thus, the test results comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification. This general trend was an unexpected result of the addition of a substituent on the piperazine ring, which is not taught or suggested by the calcium antagonists disclosed in references AW or AY, taken alone or in combination.

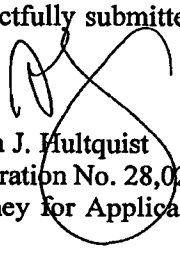
Thus, references AW and AY do not teach or suggest the compounds of the present invention, as claimed, which is directed to opioid diarylmethylpiperazines and piperidines in which there is a substituent attached to at least one of the carbon atoms in the piperazine ring.

Applicants note for the record that claims 4-8, 12, 13, 18, 19, 23, 25-28, 44, 64 and 65 have been found patentable over the prior art, particularly since AS-AU, BD-BH and AM do not qualify as prior art as discussed above.

For all of the foregoing reasons, claims 1, 3-8, 12-21, 23-28, 38-40, 44, 64 and 65, as amended, are fully patentably distinguished over the references cited and are in condition for allowance.

If any issues remain outstanding in connection with the allowance of this application, the Examiner is requested to contact the undersigned attorney, at (919) 990-9531 to discuss their resolution, so that this application can be passed to issue at an early date, consistent with the substantial advance in the art achieved by the invention claimed in this application.

Respectfully submitted,



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Attorney File: 3022-107

Patent Application
3022-107

#10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al. Group Art Unit: 1202

Application No. 08/284,445 Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: **"OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature

MARY B. CARUSO
Name of Person Mailing This Paper

FEBRUARY 9, 1996
Date of Mailing

EG581244813US
Express Mail Label Number

DECLARATION OF DR. ROBERT MCNUTT
UNDER 37 C.F.R. Section 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Robert Walton McNutt, Jr., hereby declare and state the following:

1. I am a citizen of the United States of America, residing at 700 Morreene Road, Durham, NC 27705, and hold a Ph.D. in organic chemistry from Boston College, granted in 1977, and I have been employed by Burroughs Wellcome, now Glaxo Wellcome, since 1979 and continuing to date, currently holding the position of Research Scientist in such company.

2. I am an inventor of subject matter described and claimed in United States Patent Application Serial No. 08/284,445 filed 03 August 1994 in the names of Kwen-Jen Chang, Grady Evan Boswell, Dulce Garrido Bubacz, Mark Allan Collins, Ann Otstot Davis, and Robert Walton McNutt, Jr. (and hereinafter referred to as the "Application").

3. I am aware that the United States Patent and Trademark Office has issued an Office Action dated 09 August 1995 in the Application, and that in such Office Action, among other rejections, claims 1, 3, 14-17 and 38-40 were rejected under 35 U.S.C. Section 102(b) as anticipated by references AW and AY, and claims 20, 21 and 24 were rejected as obvious in view of references AW and AY. References AW and AY are as follows:

AW Iwamoto et al., "Calcium Antagonism by KB-2796, a New Diphenylpiperazine Analogue, in Dog Vascular Smooth Muscle," J. Pharm. Pharmacol. 43, 535-539, 1991 ("Iwamoto I"); and

AY Iwamoto et al., "Effects of KB-2796, a New Calcium Antagonist, and Other Diphenylpiperazines on [3H]Nitrendipine Binding," J. Pharmacol., 48, 241-247 (1988) ("Iwamoto II").

4. I have read and am familiar with the references identified in Paragraph 3 above.

5. The references identified in Paragraph 3 above disclose the following compounds:

"Compound A": 3-(4-chloro-α-(4-(3- methylbenzyl)piperazinyl)benzyl)phenol;

"Compound B": 1-(bis(4-methoxyphenyl)methyl)-4-(2,3,4-trimethoxybenzyl)piperazine;

"Compound C": 1-(bis(4-fluorophenyl)methyl)-4-(3-(2,3,4- trimethoxyphenyl)-2-propen-1-yl)piperazine;

KB-2796: 1-bis(4-fluorophenyl)methyl)-4-(2,3,4- trimethoxybenzyl)piperazine;

Flumarizine: 1-(bis(4-fluorophenyl)methyl)-4-(3-phenyl-2- propen-1-yl)piperazine; and

Cinnarizine: 1-(diphenylmethyl)-4-(3-phenyl-2-propen-1- yl)piperazine.

6. None of the compounds disclosed in Iwamoto I or II, as identified in Paragraph 5 above, have any substituents attached to any of the carbon atoms in the piperazine ring.

7. I have collaborated on tests conducted on certain diphenylpiperazine compounds using the assay procedures set out in Example 92 on pages 156-157 of the specification of the Application. These tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II and identified in Paragraph 5 above, had no substituents on the carbon atoms of the piperazine ring. The other compound of the pair was the same as the first except that it had two methyl groups on the carbon atoms of the piperazine ring.

8. The compounds tested according to Paragraph 7 were as follows, wherein Compounds 1-4 have no substituents on the carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on the carbon atoms of the piperazine ring:

Compound 1: (±)-3-(α-(4-Allyl-1-piperazinyl)-4- chlorobenzyl)phenol;

Compound 1a: (±)-3-((αR*)-α-((2S*,5R*)-4-Allyl-2,5- dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (±)-3-(α-(4-Allyl-1-piperazinyl)-4- bromobenzyl)phenol;

Compound 2a: (±)-3-((αR*)-α-((2S*,5R*)-4-Allyl-2,5- dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (±)-3-(α-(4-Allyl-1- piperazinyl)benzyl)phenol;

Appendix I - Continued

Compound 3a: (±)-3-((αR*)-α-((2S*,5R*)-4-Allyl-2,5- dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (±)-3-(α-(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (±)-3-((αR*)-α-((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

9. The test results for Compounds 1-4 and Compound 1a- 4a described in Paragraphs 7-8, using assays described in Example 92 on pages 156-157 of the specification of the Application, are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

nd = not determined

*Test results showed that Compound 2 has antagonistic activity rather than agonist activity in the mouse vas deferens assay

10. The test results listed in Paragraph 9 above show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred

times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

11. The test results in Paragraphs 9 and 10 above comparing compounds in which the piperazine ring is substituted with two methyl groups on the carbon atoms with those that do not have a substituent on any of the carbon atoms of the piperazine ring show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification of the Application.

All statements made herein of my own knowledge are true, and all statements made on inference and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Robert Walton McNutt, Jr.

Dr. Robert Walton McNutt, Jr.

Date: February 7, 1996

AstraZeneca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **ROBERTS ET AL.**	Filed: **November 17, 2003**
Application No: **10/714,447**	Attorney Docket No.: **A1479-3P US**
Art Unit: **1624**	Examiner: **Emily Bernhardt**
Title: **Novel Compounds with Analgesic Effects**	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TERMINAL DISCLAIMER (By Attorney of Record)

Assignee, AstraZeneca Canada Inc., duly organized under the laws of Canada and having its principal place of business at 1004 Middlegate road, Mississauga, Ontario L4Y 1M4, Canada, is the assignee of the entire right, title, and interest in and to the above-identified Application No. 10/714,447, filed November 17, 2003 for Novel Compounds with Analgesic Effect in the names of Edward Roberts, Niklas Plobeck, and Claes Wahlestedt, as indicated by assignments duly recorded in the United States Patent and Trademark Office at Reel/Frame 9531/0722 on April 24, 1997, Reel/Frame 9232/0471 on September 24, 1998, and at Reel/Frame 011217/0591 on October 12, 2000.

To obviate a double patenting rejection, the terminal part of the statutory term of any patent granted on the instant application that would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior patent No. 6,696,447 is hereby disclaimed, except as provided below. Any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§ 154 to 156 and 173 of the prior patent, as presently shortened by any terminal

disclaimer, is not disclaimed in the event that the prior patent later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or in part, is terminally disclaimed under 37 C.F.R. § 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated before the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Please charge the $130.00 fee due in accordance with 37 C.F.R. § 1.20(d) to Deposit Account No. 26-0166, referencing Attorney Docket No. A1479-3P US.

The undersigned is an attorney of record.

Respectfully submitted,

Global Intellectual Property, Patents,
AstraZeneca,
1800 Concord Pike,
Wilmington, DE-19850-5437
Phone No: 302-885-4269

/Jacqueline M. Cohen/
Name: Jacqueline M. Cohen
Dated: December 3, 2007
Reg. No: 51,574

APPENDIX C
RELATED PROCEEDINGS APPENDIX

None.

APPENDIX D
LIST OF REFERENCES RELIED ON BY EXAMINER

1) WO93/15062.

2) U.S. Pat. No. 5,658,908.

3) Bilsky, et al., "Characterization of Enantiomers of (±)BW373U86 and Related Compounds: Highly Selective Nonpeptidic Delta Opioid Agonists," *Reg. Peptides* 54:25-26(1994)—**Cited as C1 in Applicants' November 17, 2003 IDS.**

4) Bilsky, et al., "SNC 80, A Selective, Nonpeptidic and Systemically Active Opioid Delta Agonist," *J. Pharmacol. Exper. Therap.* 273:359-366 (1995)—**Cited as C2 in Applicants' November 17, 2003 IDS.**

5) Calderon, et al., "Probes for Narcotic Receptor Mediated Phenomena. 19. Synthesis of (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-Dimethyl-1-Piperazinyl)-3-Methoxybenzyl]-N,N-Diethylbenzamide (SNC 80): A Highly Selective, Nonpeptide Δ Opioid Receptor Agonist," *J. Med. Chem.* 37:2125-2128 (1994)—**Cited as C4 in Applicants' November 17, 2003 IDS.**

6) Calderon, et al., "Probes for Narcotic Receptor Mediated Phenomena. 23. Synthesis, Opioid Receptor Binding, and Bioassay of the Highly Selective δ Agonist (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-Dimethyl-1-Piperazinyl)-3-Methoxybenzyl]-N,N-Diethylbenzamide (SNC 80) and Related Novel Nonpeptide Δ Opioid Receptor Ligands," *J. Med. Chem.* 40:695-704 (1997)—**Cited as C5 in Applicants' November 17, 2003 IDS.**

7) U.S. Patent No. 6,696,447.